Systematic Review and Meta-Analysis

Medicine

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Efficacy of albumin with diuretics in mechanically ventilated patients with hypoalbuminemia

A systematic review and meta-analysis

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Abstract

Background: Hypoalbuminemia is associated with fluid overload, the development of acute respiratory distress syndrome, and mortality. The co-administration of albumin and diuretics for the treatment of patients with hypoalbuminemia is expected to increase urine output, without hemodynamic instability, and improve pulmonary function; however, these effects have not been systematically investigated. Here, we aimed to clarify the benefits of the co-administration of albumin and diuretics in mechanically ventilated patients.

Methods: We searched for randomized, placebo-controlled trials that investigated the effects of the co-administration of albumin and diuretics compared with placebo and diuretics, in mechanically ventilated patients with hypoalbuminemia. We searched these trials in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via PubMed, and EMBASE databases. Primary outcomes were hypotensive events after the intervention, all-cause mortality, and the length of mechanical ventilation. Secondary outcomes were improvement in the ratio of partial pressure arterial oxygen and fraction of inspired oxygen (P/F ratio) at 24 hours, total urine output (mL/d), and the clinical requirement of renal replacement therapy (RRT).

Results: From the 1574 records identified, we selected 3 studies for quantitative analysis. The results of albumin administration were as follows: hypotensive events (risk ratio [RR] 0.33 [95% CI: 0.15 -0.81]), all-cause mortality (RR 1.0 [95% CI: 0.45–2.23]), the length of mechanical ventilation in days (mean difference –0.34 [95% CI: –1.99 to 1.31]), and improvement in P/F ratio (RR 2.83 [95% CI: 1.42–5.67]). None of the randomized controlled trials reported the total urine output, and one reported that no participants required RRT. Adverse events were not reported during the trials. The certainty of evidence was low (in the hypotensive events after the intervention and all-cause mortality) to moderate (in the length of mechanical ventilation in days, improvement of P/F ratio, clinical requirement of RRT, and adverse events).

Conclusions: Although this treatment combination reduced the number of days for which mechanical ventilation was required, it did not reduce the all-cause mortality at 30 days. In conclusion, the co-administration of albumin and diuretics may reduce hypotensive events and improve the P/F ratio at 24 hours.

Abbreviations: ARDS = acute respiratory distress syndrome, CI = confidence interval, RCT = randomized controlled trial, RR = risk ratio, RRT = renal replacement therapy.

Keywords: albumin, acute respiratory distress syndrome, diuretics, hypoalbuminemia, mechanical ventilation

1. Introduction

Hypoalbuminemia is frequently observed in critically ill patients,[1–3] in whom severe inflammation can increase capillary permeability, leading to albumin exudation from intravascular to extravascular compartments,[1] which leads to hemodynamical instability such as hypovolemic shock. To maintain organ perfusion, fluid resuscitation is frequently performed.[4] However, with the increasing occurrence of capillary permeability, excessive fluid resuscitation leads to non-cardiogenic pulmonary edema. This is the dilemma that critically ill patients suffer as a result of their pathophysiological status.[5]

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Thus, hypoalbuminemia is also correlated with fluid overload and the development of acute respiratory distress syndrome (ARDS), which require mechanical ventilation.[2,3]

Albumin is one of the major determinant factors of vascular colloid oncotic pressure and, as such, the administration of albumin in critically ill patients with hypoalbuminemia is reasonable to maintain or increase intravascular volume to maintain organ perfusion. Therefore, colloids, such as albumin, may suppress the amount of infusion volume required compared with crystalloids.[6] A meta-analysis concluded that the use of albumin for the resuscitation of patients with sepsis is associated with lower mortality than the use of other fluid resuscitation methods.[7]

The ARDS Clinical Trials network reported a randomized controlled trial (RCT), which showed that conservative fluid management and diuretics improve lung function and reduce the length of mechanical ventilation.[8] Although diuretic administration can improve ARDS by volume reduction, there is a risk of hemodynamic instability in critically ill patients. However, the combined use of albumin and diuretics may negate the effect of diuretics alone by maintaining hemodynamic stability. It has also been hypothesized that when the plasma albumin complex is bound to furosemide, it reaches the proximal tubular cells to act in the ascending limb of the loop of Henle.[9] Thus, albumin, in combination with diuretics, may contribute to an increased urine output.

The effects of the co-administration of albumin and diuretics for critically ill patients with hypoalbuminemia have been investigated in several RCTs.[10–15] However, to date, no systematic review and meta-analysis of this treatment in mechanically ventilated patients has been carried out.

In the present study, we aimed to clarify the benefits of the co-administration of albumin and diuretics for mechanically ventilated patients. The findings of this systematic review and meta-analysis could provide frontline physicians with efficacy information for the co-administration of albumin and diuretics in critically ill patients with ARDS and hypoalbuminemia.

2. Methods

2.1. Compliance with reporting guidelines

We conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[16] and the recommendations listed in the Cochrane Handbook.[17]

2.2. Research question and eligibility criteria

The research question of the present study was "effectiveness of co-administration of albumin and diuretics in mechanically ventilated patients with hypoalbuminemia." A patient was defined as mechanically ventilated when there was a possibility of fluid overload and confirmed hypoalbuminemia (serum albumin under 3.0 mg/dL). The intervention was defined as the co-administration of albumin and diuretics. Control groups were defined as those that received the placebo or no intervention with diuretics. All placebo treatments contained 0.9% sodium chloride solution with same amount as albumin. We did not consider the length of albumin administration or concentration. We included only RCTs and did not consider publication status, date, language, or country. We excluded quasi RCTs, cross-over trials, and cluster randomized trials.

2.3. Outcomes of interest

The primary outcomes of interest were hypotensive events after the intervention (duration of the event was defined within 7 days after the intervention; considerable range for analysis was 0–10 days), all-cause mortality at 30 days, and the length of mechanical ventilation (from tracheal intubation to extubation). Initially, we defined a hypotensive event as a systolic blood pressure ≤90 mm Hg. However, the blood pressure is physiologically different between pediatric and adult populations. To include pediatric patients, we included the hypotensive events (no specific data for blood pressure) reported in Reddy et al[15] Martin et al[13] reported the number of free days during the 30-day follow-up period in which the patient was not ventilated and, from this, we calculated the remaining days where they would have been under mechanical ventilation. The secondary outcomes were the improvement of the ratio of partial pressure arterial oxygen and fraction of inspired oxygen (P/F ratio) at 24 hours, the total urine output (mL/d), the clinical requirement of renal replacement therapy within 7 days, and all other adverse events.

2.4. Search strategy and selection of studies

The following databases were searched: the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE via PubMed; and EMBASE. The following databases were also searched for ongoing or unpublished trials: the World Health Organization International Clinical Trials Platform Search Portal; and ClinicalTrials.gov. The detailed search strategy is shown in Protocols.io (https://www.protocols.io/view/the-efficacy-of-albumin-with-diuretics-in-the-mech-bpadmia6). Researchers also searched for other relevant studies to include. After the removal of duplicate studies, articles were independently screened by checking title and abstract information using Rayyan.[18]

2.5. Data extraction

The extraction of data was performed by 2 reviewers independently, and any disagreement was resolved by a third reviewer, if required. We asked the relevant author for further data on unreported outcomes, if the data were unavailable.

In studies where the authors reported the continuous data as median and interquartile range, we converted the indicated values to mean ± standard deviation according to the Cochrane Handbook for Systematic Reviews of Interventions.[17]

2.6. Dealing with missing data

For missing data, we contacted the relevant author within 2 weeks via email. If no response was received, we followed up the initial email a maximum of 2 times. We did not include studies that lacked information that we were unable to source from the author.

2.7. Quality assessment

Two researchers independently used a tool for assessing the risk of bias in randomized trials.[19] To summarize the evidence, we followed the Grading of Recommendations, Assessment, Development and Evaluation approach, and Summary of Findings tables[20] for the outcomes of interest.

2.8. Statistical analysis

The Review Manager software (RevMan 5.4, Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) was used to carry out the meta-analysis.[21] We used a random-effects model and reported the results of outcomes as mean difference and risk ratio (RR). Effect sizes are reported as 95% confidence intervals (CI) and results are reported graphically by forest plots. Simultaneously, we calculated I^2 (I^2 values of 0% to 40%: may not be important; 30% to 60%: may represent

moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity). Cochrane χ^2 test (Q-test) was used to investigate I^2. Statistical differences were considered significant at a P value <.10.

2.9. Ethics and dissemination

According to the nature of this study, no ethical approval was required. This study was registered in Protocols.io (https://www.protocols.io/view/the-efficacy-of-albumin-with-diuretics-in-the-mech-bpadmia6).

3. Results

3.1. Search results and characteristics of included trials

We identified 1574 records during the search conducted in October 2020. Seven RCTs were identified and assessed for their eligibility for this study; one article was excluded as no outcome of interest was included (PRISMA 2020 flow diagram). We finally included 3 RCTs (n = 129) that fulfilled all the eligibility criteria.[13–15]

The RCTs were carried out in the USA, Canada, and India (Table 1). The mean age of the patients ranged from 3.6 to 48.9 years, with sample sizes of 40 to 45 per study. One of the studies included only children.[15]

In these studies, 20% or 25% albumin was used. Furosemide was the diuretic used in these studies, although doses and intravenous infusion method (continuous or bolus) were different among the trials (Table 1). Ventilation days were recorded in the studies conducted in Canada and India. We calculated the ventilator days as 28 days minus the ventilator-free days recorded in the Indian study. Mean and standard deviation were calculated using each available number. Reddy et al[15] reported median number (albumin median 3 [2, 5] vs placebo median 4 [2, 8]). Oczkowski et al[14] reported the mean of the total time on ventilation in hours (albumin median 334 [176.5, 627.0] vs placebo median 332 [245, 515]).[22,23]

P/F ratios of treatment and control patients were as follows: United States (162, 182), India (288, 256). Use of concurrent drugs, such as catecholamines, were not sufficiently recorded. Detailed urine output was not recorded. APACHE II score of treatment and control patients were as follows: United States (13.4, 14), Canada (14.83, 13.38).

Figures 1 and 2 show the risk of bias for each outcome in included studies, ranging from low to high.

3.2. Primary outcomes

Table 2 shows the summary of findings of the present study. Although there was low certainty and risk of bias of missing outcomes, hypotensive events were recorded in all 3 RCTs.[13–15] Compared with placebo, albumin reduced hypotensive events (RR 0.33 [95% CI: 0.15–0.81]; Fig. 3A). In the overall risk of bias for hypotensive events, the study of high risk of bias was 33%, the study of some concerns was 33%, and the study of low risk of bias was 33% (Fig. 1A).

The number of mechanical ventilation days was measured in 2 RCTs with moderate certainty of the evidence.[14,15] The result of the meta-analysis did not clarify the effect of albumin in reducing the number of mechanical ventilation days (mean difference −0.34 [95% CI: −1.99 to 1.31]; Fig. 3B). In the overall risk of bias for the effect of albumin in reducing the number of mechanical ventilation days, the study with high risk of bias was 50% and the study with low risk of bias was 50% (Fig. 1B). All-cause mortality was recorded in all trials, and the results were not different (RR 1.0 [95% CI: 0.45 to 2.23]; Fig. 3C). In the overall risk of bias for the all-cause mortality, the study

Table 1

All included randomized controlled trials.

Study	Region	Study participants	Number of participants (male, female)	Age, mean (SD)	Intervention	Reported outcome of interest	Primary outcome of the original study
Martin et al (2005)[13]	United States	Acute lung injury/acute respiratory distress syndrome Serum total protein concentrations were <6.0 g/dL	40 (19, 21)	Placebo 46.4 (18) Albumin 48.9 (21.6)	Placebo vs 25% albumin	The hypotensive event after intervention, all-cause mortality, the length of mechanical ventilation days, the clinical requirement of renal replacement therapy within 7 d, all adverse events	Change in oxygenation over a 24-h period
Oczkowski et al (2018)[14]	Canada	Hemodynamically stable patients with hypoalbuminemia	45 (29, 16)	Placebo 64.7 (15.2) Albumin 61.71 (17.2)	Placebo vs 25% albumin twice daily for up to 6 doses	The hypotensive event after intervention, all-cause mortality, the length of mechanical ventilation days, the clinical requirement of renal replacement therapy, all adverse events	Feasibility
Reddy (2018)[15]	India	Critically ill mechanically ventilated hypoalbuminemic children with fluid overload	44 (35, 9)	Placebo 3.61 (3.13) Albumin 2.77 (3.3)	Placebo vs 20% albumin (5 mL/kg) single dose over 6 h with furosemide infusion for 48 h	The hypotensive event after intervention, all-cause mortality at 30 d, the length of mechanical ventilation days	28-d ventilation free days

SD = standard deviation.

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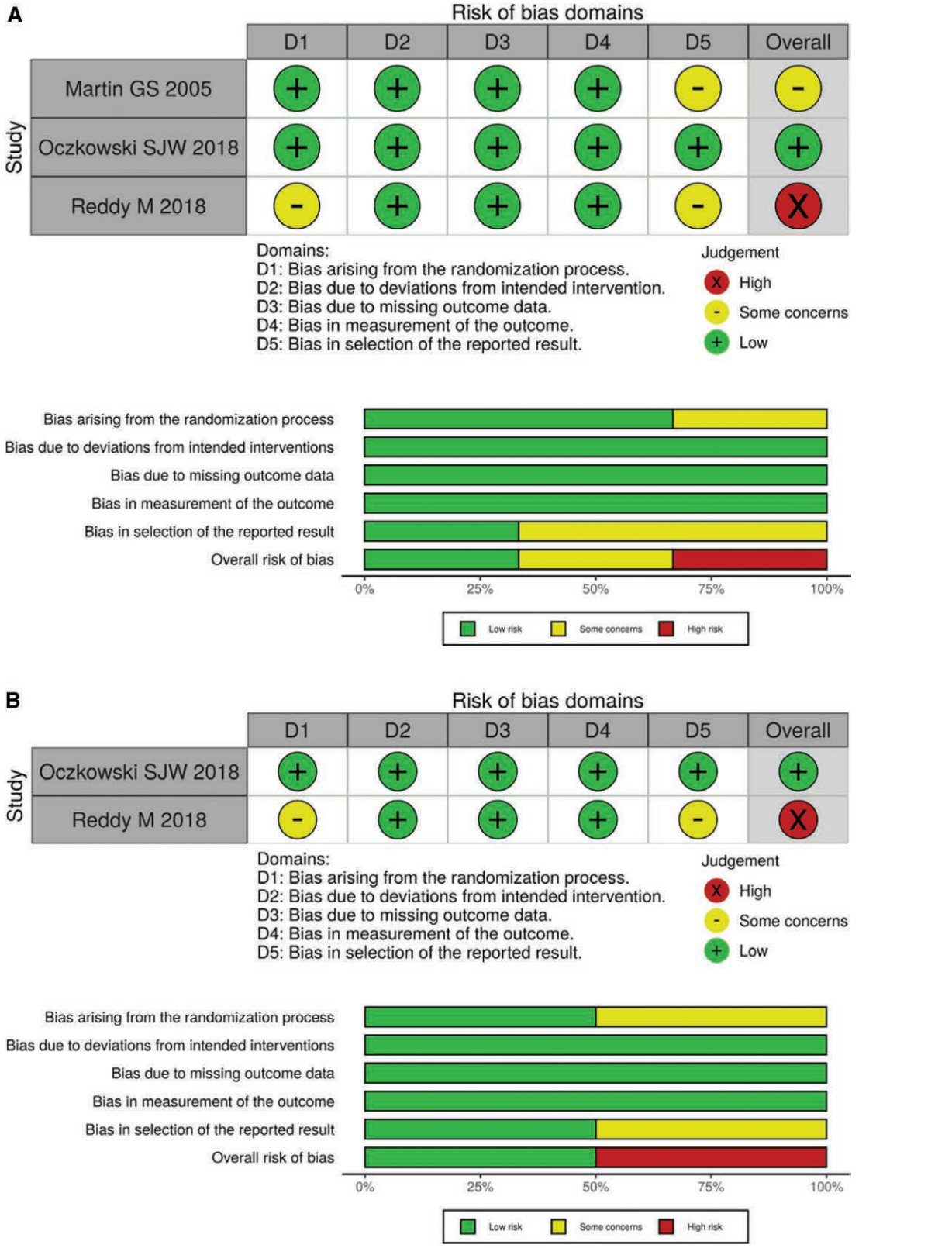

Figure 1. Risk of bias assessment for indicated primary outcomes. (A) Hypotensive events. (B) Duration of mechanical ventilation (in days). (C) All-cause mortality.

with some concerns was 33% and the study with low risk of bias was 33% (Fig. 1C). We were not able to carry out pre-specified sensitivity analyses for the primary outcomes, or subgroup analysis because the number of the RCTs was insufficient.

3.3. Secondary outcomes

There was a moderate certainty of evidence in the secondary outcomes (Table 2). One RCT recorded the change of P/F.[13] They found that, compared with placebo, albumin infusion improved the P/F ratio (RR 2.83 [95% CI: 1.42–5.67]; Fig. 4). In the overall

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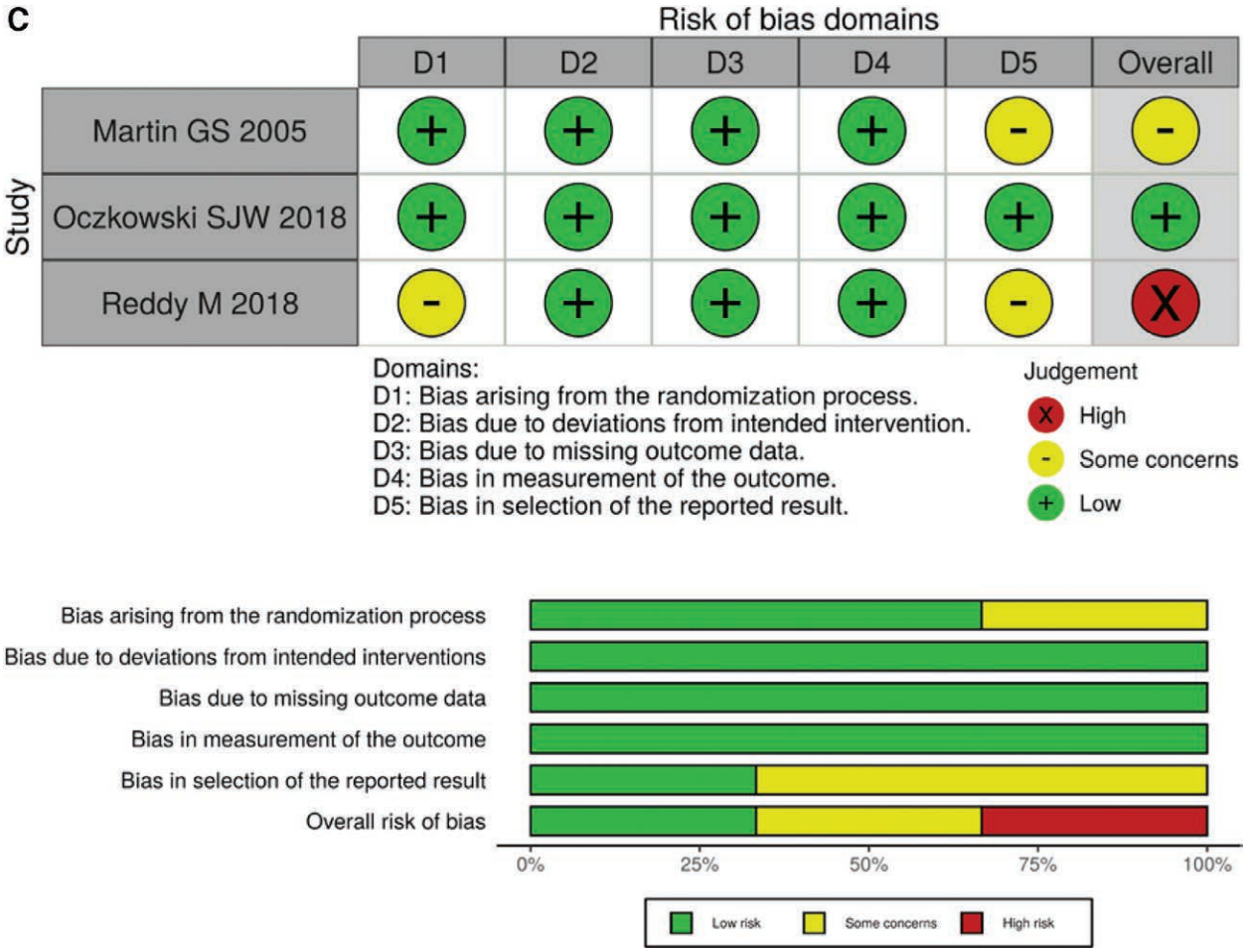

Figure 1. Continued

risk of bias for the P/F ratio, the study with some concerns was 100%. No RCTs reported the total urine output (mL/d) after the intervention. One RCT reported that no participants required renal replacement therapy. Adverse events were not reported during any of the trials. We were not able to carry out pre-specified sensitivity analyses for the secondary outcomes or subgroup analysis because the number of the RCTs was insufficient.

4. Discussion

The results of this systematic review and meta-analysis covered 3 RCTs and showed that albumin treatment in combination with diuretics may result in a large reduction in the number of hypotensive events. It also likely results in an improvement in the P/F ratio at 24 hours (considerable range for analysis is 12 hours to 7 days) after the intervention. Albumin with diuretics likely reduced the number of mechanical ventilation days. However, the evidence suggests that albumin with diuretics does not decrease all-cause mortality at 30 days.

A large reduction in hypotensive events following the co-administration of albumin and diuretics may result from maintaining the intravascular volume by albumin administration. As albumin determines the vascular colloid oncotic pressure, the exudation of the intravascular fluids might be reduced by albumin. We did not use mean arterial pressure as a primary outcome because continuous valuables were not measured in these RCTs. Furthermore, the threshold value was set at 90 mm Hg in adults. However, in pediatric patients who have different normal physiological vital signs, it is difficult to integrate the data. Thus, we speculate that binary variables (the presence of hypovolemic event) are adequate for evaluating the effect of albumin on hemodynamic state.

A P/F improvement and a reduction in the number of days of mechanical ventilation were found following the co-administration of albumin and diuretics. We speculate that this result is strongly related to the reduced number of hypotensive events. Albumin administration might maintain the intravascular volume by increasing the vascular colloid oncotic pressure. Therefore, the number of hypotensive events and total amount of fluid infused were reduced. This volume reduction may have improved the oxygenation of the mechanically ventilated patient.

Although the co-administration of albumin and diuretics reduced the number of mechanical ventilation days, the all-cause mortality rate did not improve. We speculate that owing to the patients having various underlying diseases and complications, the co-administration of albumin and diuretics could not directly improve the all-cause mortality. However, a reduction in the number of ventilation days seems to be effective for minimizing complications such as ventilator-associated pneumonia or deep vein thrombosis.[24,25]

The clinical implication of this study was that co-administration of albumin with diuretics may be used in clinical settings to improve P/F ratio, and reduce hypotensive events and mechanical ventilation days in mechanically ventilated patients with hypoalbuminemia and a hemodynamically stable status. The variability of the certainty of evidence from low to moderate is attributed to the small sample size and concerns about risks of biases. In the future, further large and well-designed RCTs should be performed.

As the included studies were <10, we did not perform tests for funnel plot asymmetry for evaluating the publication bias.[17]

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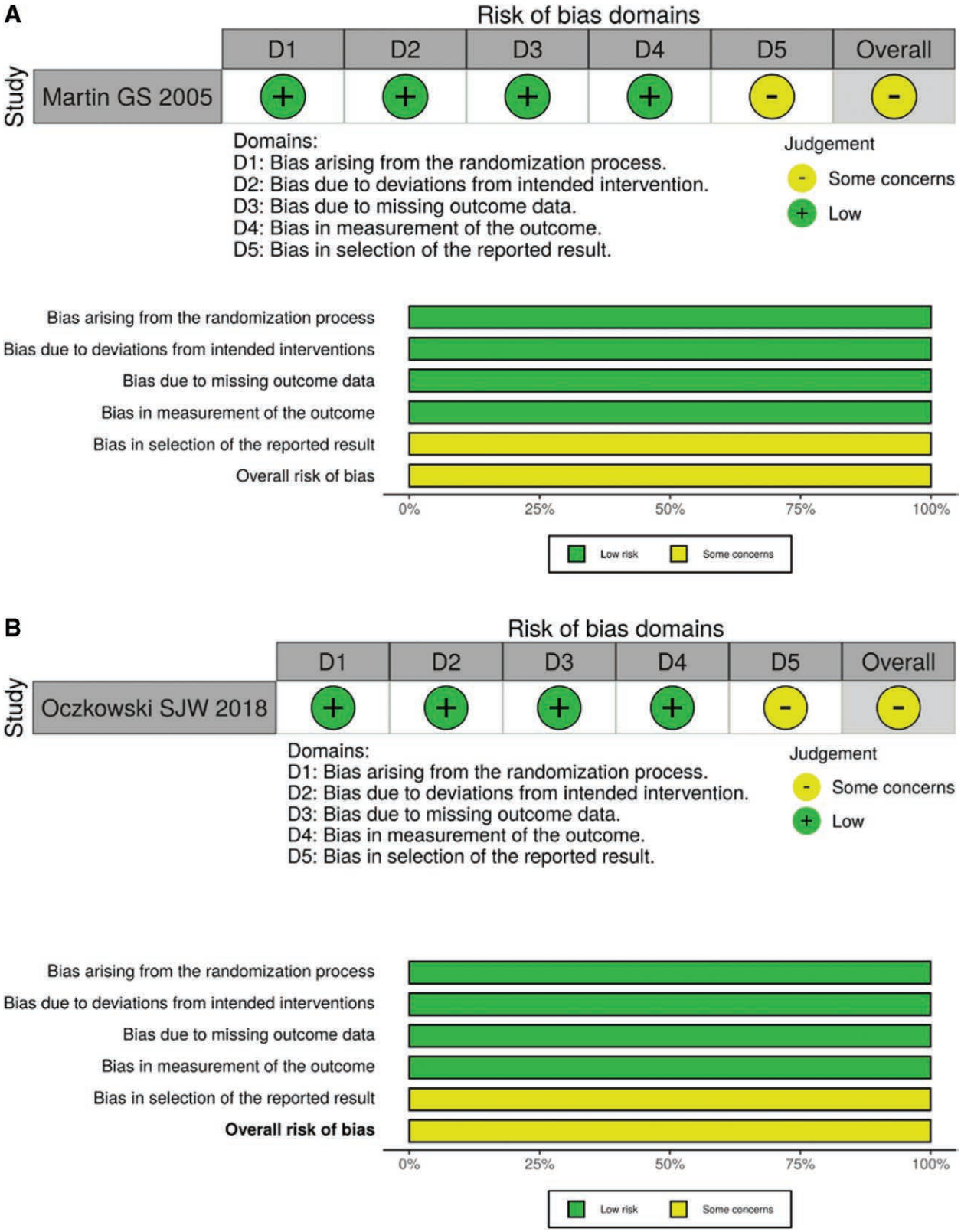

Figure 2. Risk of bias assessment for indicated secondary outcomes. (A) Improvement of P/F ratio at 24 h (considerable range for analysis is 12 h to 7 d) after the intervention. (B) Clinical requirement of renal replacement therapy within 7 d (considerable range for analysis will be 1–30 d). (C) All adverse effects.

However, we tried to certify the publication bias by searching the ongoing studies, which resulted in any other ongoing studies.

The present systematic review and meta-analysis has several limitations. First, we included only 3 RCTs, each with various quality in terms of risk of bias. Larger RCTs are required to establish a more thorough review. Second, we were unable to carry out sensitivity analyses for outcomes owing to imprecision. However, preparing a heterogenic mechanically ventilated population is difficult owing to the nature of intensive care, which consists of many clinical variables and situations.

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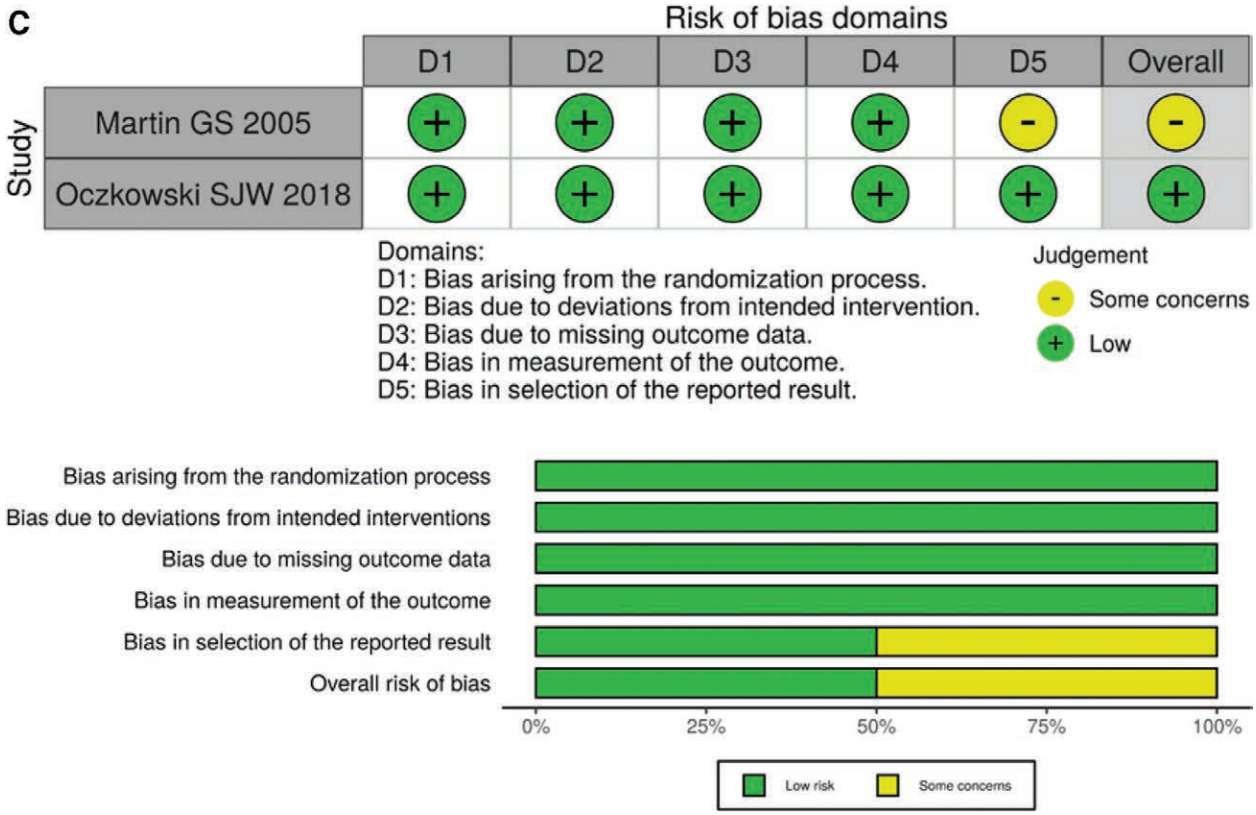

Figure 2. Continued

Table 2

Summary of findings.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no intervention with diuretics	Risk with albumin with diuretics				
Hypotensive events after intervention	270 per 1000	88 per 1000 (32 to 212)	OR 0.26 (0.09–0.73)	129 (3 RCTs)	⨁⨁◯◯ Low†‡	Albumin with diuretics may result in a substantial reduction in hypotensive events after intervention
Number of mechanical ventilation days	The duration of mechanical ventilation days was 4.71–14.37	MD 0.34 lower (1.99 lower to 1.31 higher)	-	89 (2 RCTs)	⨁⨁⨁◯ Moderate†‡	Albumin with diuretics likely reduce the length of mechanical ventilation days
All-cause mortality at 30 d	206 per 1000	211 per 1000 (83–444)	OR 1.03 (0.35–3.07)	129 (3 RCTs)	⨁⨁◯◯ Low†‡	The evidence suggests that albumin with diuretics does not decrease all-cause mortality at 30 d
Improvement of P/F ratio at 24 h (considerable range for analysis is 12 h to 7 d) after intervention	300 per 1000	850 per 1000 (545 to 964)	OR 13.22 (2.79–62.67)	40 (1 RCT)	⨁⨁⨁◯ Moderate‡	Albumin with diuretics likely results in a large increase in the improvement of P/F ratio 24 h (considerable range for analysis is 12 h to 7 d) after intervention
Clinical requirement of renal replacement therapy within 7 d (considerable range for analysis is 1–30 d)	0 per 1000	0 per 1000 (0–0)	Not estimable	45 (1 RCT)	⨁⨁⨁◯ Moderate‡§	Albumin with diuretics likely results in little to no difference in the clinical requirement of renal replacement therapy within 7 d (considerable range for analysis is 1–30 d)
All adverse events	Not pooled	Not pooled	Not pooled	85 (2 RCTs)	⨁⨁⨁◯ Moderate†‡	Albumin with diuretics is not likely to increase all adverse events

Albumin with diuretics compared to placebo or no intervention with diuretics for mechanically ventilated patients with hypoalbuminemia. Patient or population: mechanically ventilated patients with hypoalbuminemia; setting: intensive care unit; intervention: albumin with diuretics; comparison: placebo or no intervention with diuretics. GRADE Working Group grades of evidence. High certainty: we are very confident that the true effect lies close to the estimated effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimated effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimated effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimated effect.

CI = confidence interval, MD = mean difference, OR = odds ratio.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

†Moderate risk of bias associated with unclear information from intended interventions and missing outcome data.

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§Moderate risk of bias associated with unclear risk of bias for the result selected from a pre-specified plan.

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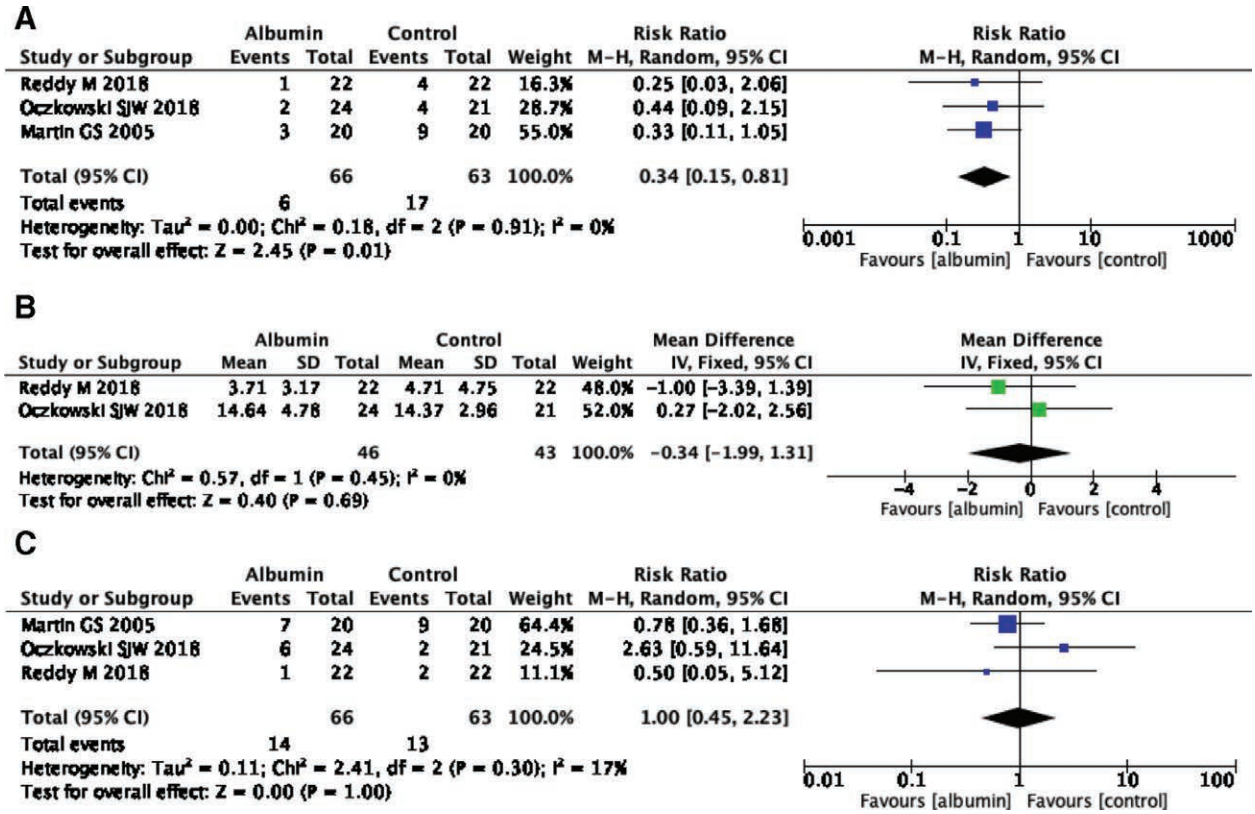
A
Albumin
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Reddy M 2018 1 22 4 22 16.3% 0.25 [0.03, 2.06]
Oczkowski SJW 2018 2 24 4 21 28.7% 0.44 [0.09, 2.15]
Martin GS 2005 3 20 9 20 55.0% 0.33 [0.11, 1.05]
Total (95% CI) 66 63 100.0% 0.34 [0.15, 0.81]
Total events 6 17
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 2.45 (P = 0.01)
0.001 0.1 1 10 1000
Favours [albumin] Favours [control]
B
Albumin
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Reddy M 2018 3.71 3.17 22 4.71 4.75 22 48.0% -1.00 [-3.39, 1.39]
Oczkowski SJW 2018 14.64 4.78 24 14.37 2.96 21 52.0% 0.27 [-2.02, 2.56]
Total (95% CI) 46 43 100.0% -0.34 [-1.99, 1.31]
Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
-4 -2 0 2 4
Favours [albumin] Favours [control]
C
Albumin
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Martin GS 2005 7 20 9 20 64.4% 0.78 [0.36, 1.68]
Oczkowski SJW 2018 6 24 2 21 24.5% 2.63 [0.59, 11.64]
Reddy M 2018 1 22 2 22 11.1% 0.50 [0.05, 5.12]
Total (95% CI) 66 63 100.0% 1.00 [0.45, 2.23]
Total events 14 13
Heterogeneity: Tau² = 0.11; Chi² = 2.41, df = 2 (P = 0.30); I² = 17%
Test for overall effect: Z = 0.00 (P = 1.00)
0.01 0.1 1 10 100
Favours [albumin] Favours [control]

Figure 3. The results of the meta-analysis of primary outcomes. (A) Hypotensive events. (B) Duration of mechanical ventilation (in days). (C) All-cause mortality. CI = confidence interval.

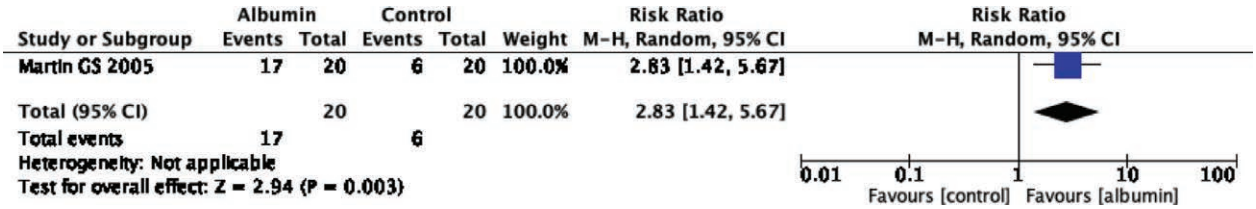
Albumin
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Martin GS 2005 17 20 6 20 100.0% 2.83 [1.42, 5.67]
Total (95% CI) 20 20 100.0% 2.83 [1.42, 5.67]
Total events 17 6
Heterogeneity: Not applicable
Test for overall effect: Z = 2.94 (P = 0.003)
0.01 0.1 1 10 100
Favours [control] Favours [albumin]

Figure 4. The results of meta-analysis of the secondary outcome, P/F ratio. CI = confidence interval.

5. Conclusions

In conclusion, the present study indicates that albumin, when administered alongside diuretics, reduced hypotensive events and led to an improvement in the P/F ratio at 24 hours. Although it is likely that co-administration reduced the number of mechanically ventilated days, the intervention did not decrease all-cause mortality at 30 days. Further large and well-designed RCTs are required to confirm the effectiveness of the co-administration of albumin and diuretics in mechanically ventilated patients.

Author contributions

YI is the guarantor. YI, NY, KY, MB, RM, and MH drafted the manuscript. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. YI, NY, KY, MB, and RM developed the search strategy. YI, NY, KY, MB, RM, and YK provided statistical expertise. MB and RM provided expertise on YI. All authors read the manuscript, provided feedback, and approved the final manuscript.

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Correction

When originally published, the risk ratio and mean difference were written incorrectly in the abstract, but correct in the body of the paper. "Risk ratio [RR] –1.05 [95% confidence interval {CI}: 0.15 -0.81]" has been corrected to "[RR] 0.33 [95% CI: 0.15 -0.81]". "Mean difference –1.05 [95% CI: –3.35 to 1.26]" has been corrected to "mean difference –0.34 [95% CI: –1.99 to 1.31]".

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